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HERITABLE SKIN DISORDERS – NOVEL MUTATIONS AND SPECTRUM OF PHENOTYPES

Genodermatoses comprise a group of phenotypically diverse conditions with variable degrees of skin involvement. In some diseases, there is only a minor, occasionally cosmetic, involvement of the skin, hair, and/or nails, whereas in other conditions, skin manifestations can be part of a severe multisystem disorder with significant morbidity and even mortality. Over the past decade or so, with the advent of molecular genetics in general, spectacular progress has been made in understanding the genetic basis of many heritable skin diseases, and in fact, mutations have now been identified in about two hundred distinct genes in these diseases (see Pulkkinen *et al*, 2002). Examination of the mutation database in these diseases has revealed a number of both predictable and surprising genes. In several conditions, the mutated genes could have been predicted on the basis of clinical, histopathologic, immunohistochemical and/or ultrastructural analysis. Such an example as epidermolysis bullosa, a group of blistering diseases with fragility of skin at the dermal/epidermal basement membrane zone. It was initially postulated that the structural genes expressed at the dermal/epidermal junction could serve as candidate genes, and this hypothesis has now been verified by demonstration of a large number of distinct mutations in as many as 10 different genes expressed within the cutaneous basement membrane zone. At the same time, a number of mutated genes have turned out to be rather surprising, and the exact relationship of the mutations in the affected genes and their consequences at the clinical and morphological level are not well understood. An example of such a condition is pseudoxanthoma elasticum, characterized by progressive calcification of elastic fibers of the skin, eyes, and the cardiovascular system. The mutated gene, ABCC6, which encodes the MRP6 protein, a putative ATP-dependent transmembrane transporter of unknown function, is expressed primarily, if not exclusively, in the liver and in the kidneys, and consequently, the pathomechanisms of this disease remain unexplained (see Uitto *et al*, 2002).

In this issue of the *Journal*, two articles deal with mutations in single-gene Mendelian disorders, both of which are phenotypically pleiotropic but involve skin. First, Martinez-Mir *et al* (2003) have examined families with multiple cutaneous and uterine leiomyomas (MCUL), a disorder inherited in an autosomal dominant pattern. There is considerable variability in the number of tumors arising from the arrector pili muscle of hair follicles, and the age of onset of the skin lesions is usually between the second and fourth decade of life. Most females develop uterine myomas, and in some families there is predisposition to renal cell carcinoma. The disease causing gene was initially mapped to the long arm of chromosome 1, region 1q42.3-q43, and mutations were subsequently identified in the FH gene encoding fumarate hydratase, a component of the tricarboxylic acid cycle involved in energy production of the cells. Although the mechanism by which FH mutations cause leiomyomas is currently unexplained, it has been hypothesized that this enzyme acts as a selective tumor suppressor gene. It is of interest to note that autosomal recessive mutations in the same FH gene have been implicated in complete deficiency of fumarate hydratase, which presents with progressive encephalopathy and developmental delay. Interestingly, some of the carrier parents of children with recessive FH deficiency have been re-examined, and on occasion have been found to show symptoms of MCUL which were undiagnosed previously.

Martinez-Mir *et al* have now identified five families of varying ethnic backgrounds with MCUL, and a total of 16 affected individuals were available for their study. FH gene was examined by PCR amplification of all exons and flanking intronic sequences, followed by automated sequencing of the PCR products. This approach was able to identify a unique mutation in the FH gene in each of the five families, including a nonsense mutation, three missense mutations, and a 4-bp frameshift deletion mutation. Examination of the corresponding control populations did not disclose their presence in unaffected, unrelated individuals, suggesting that they are not common polymorphisms, and are therefore likely to be pathogenic. Careful examination of the clinical presentation of the affected individuals in this and a similar, previously published study failed to establish clear cut genotype/phenotype correlations, as considerable phenotypic variability regarding skin and uterine involvement was noted. Nevertheless, identification of these family specific mutations in the FH gene now allows presymptomatic screening and careful early monitoring of family members who are at risk for development of the disease.

In another paper in this *Journal*, Whittock *et al* (2003) studied X-linked dominant chondrodysplasia punctata (CDPX2; also known as the Conradi–Hünermann–Happle syndrome) which is characterized by a number of skeletal and neurologic abnormalities associated with skin lesions. The skin abnormalities include striate palmoplantar hyperkeratosis, follicular atrophoderma, and pigmentary changes that follow the lines of Blaschko. These skin lesions are often transient and may resolve even during early infancy. The condition, being X-linked dominant, is usually lethal in male embryos, although males in the context of a XXY karyotype may survive. Complicating genetic counseling is the fact that there is often a stepwise increase in disease severity from one generation to the next (known as anticipation). The gene, EBP, which harbors mutations in CDPX2, resides in the short arm of X-chromosome, region Xp11.23-p11.22, and encodes emopamil binding protein that functions as a $\Delta 8$-$\Delta 7$ sterol isomerase, a critical enzyme in the cholesterol biosynthetic pathway.

In this study, Whittock *et al* examined 11 unrelated patients with CDPX2, all having hyperkeratosis and patchy ichthyotic skin following the lines of Blaschko. There were also hair abnormalities (sparse, fine, and dry hair), cicatricial alopecia, and nail dystrophy, in addition to developmental and neurologic manifestations. The investigators were able to find mutations in the EBP gene in all patients, 7 of which are novel. Since the enzyme mutated in this condition is required for synthesis of cholesterol, it appears that hemizygous males, dependent on *de novo* cholesterol synthesis, either do not survive or survive with severe neurologic defects. On the other hand, one of the clinical

observations in this study is that the affected heterozygous females have normal mental development, indicating that a sufficient amount of cholesterol is being synthesized from the normal allele. The results of this study further confirm the diagnostic value of gas chromatography-mass spectrometry in CDPX2 for determination of elevated cholesterol precursors in serum. However, identification of mutations in the EBP gene can now be used to confirm the diagnosis at the DNA level. These findings also provide means for DNA-based prenatal diagnosis in pregnancies at risk for CDPX2.

GENETIC COMPLEXITY OF POLYGENIC DISORDERS – THE PARADIGM OF PSORIASIS

Following the great success in identifying distinct mutations in the candidate genes in an increasing number of single-gene Mendelian diseases, the emphasis is shifting towards analysis of complex genetic disorders for identification of susceptibility or protective genes. The paradigm of such conditions is psoriasis, a common disorder with apparently multifactorial etiology. Demonstrations of heritability in psoriasis date back to early 60s, including studies on the prevalence, clinical course, and genetics of psoriasis in isolated populations, such as in residents of the Faroe Island, a group of islands halfway between Norway and Iceland. Although estimates have suggested the overall heritability of psoriasis may be as high as 90%, it is clear that various environmental factors are needed for the expression of the phenotype.

During the past decade, several genome-wide linkage studies have been performed in attempts to identify putative susceptibility loci in psoriasis. There is now a consensus that a chromosomal region on the short arm of chromosome 6, locus 6p21.3, which contains the HLA-C major histocompatibility locus, is tightly linked to psoriasis in different populations; this locus has been designated as PSORS1. In addition to HLA-C, other genes within PSORS1 have shown linkage, and in fact, recent evidence has suggested that the HCR gene, encoding a putative transcription factor expressed in the epidermis, is a candidate gene in psoriasis. Nevertheless, linkage studies suggest that the PSORS1 locus accounts for less than 50% of the genetic component of psoriasis. Accordingly, psoriasis has been linked to at least 6 additional susceptibility loci (PSORS2-7) with LOD scores >3. (LOD score, logarithm of the odds, is a measure of the strength of the association between a locus and the phenotype. Formally, a LOD score >3 establishes linkage and implies that the likelihood of an association by chance is less than 1 in 1000). The difficulty in finding additional minor susceptibility loci is that the strong influence of PSORS1 can mask linkage to other loci.

In this issue, Asumalahti *et al* (2003) have examined a cohort of psoriasis patients in families that did not show linkage to PSORS1. Specifically, the investigators examined 31 Finnish families with at least three affected individuals in each family, and samples were collected from a total of 227 individuals among whom 121 were affected. A genome wide scan using microsatellite markers placed upon the genome on the average at 9.1 cM interval initially identified several potential loci on six chromosomes. However, further fine-mapping with additional markers revealed linkage to a locus on the short arm of chromosome 18, 18p11, in 9 families (LOD score 3.58). Bootstrap analysis* revealed that evidence for linkage between psoriasis and the locus on 18p was primarily contributed by a single family (no. 3 in **Table 1** of the paper), although other families also supported the locus. As expected, these families were negative for association with PSORS1 locus, and conversely, analysis of the PSORS1 positive families yielded negative scores across the 18p locus.

A previous study based on psoriasis sib pair analysis in the British population also yielded evidence for linkage to chromosome 18p. Thus, these two studies collectively establish a new susceptibility locus. Of interest is the notion that the 18p locus also harbors a susceptibility locus for atopic disease, and psoriasis and atopic disease also share other susceptibility regions on different chromosomes. These observations suggest, perhaps, that genes at these loci may have effects on dermal inflammation and immunity contributing to the psoriasis phenotype. Unfortunately, no confirmed genes have been located in the 18p susceptibility region as yet, and this study, which establishes another minor susceptibility locus in psoriasis, adds to the complexity of this complex genodermatosis.

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*Bootstrap method involves resampling of the original data by generating multiple replicate sets of data, which allows establishing the contributions of individual components of the database. In this paper, the original dataset was repeatedly resampled for LOD score calculations by sequentially excluding one of the families at a time (also known as "jack-knife estimation"). This strategy is called "bootstrap method" because to use the data to generate more data seems analogous to a trick used by the fictional Baron Münchhausen who, when he found himself at the bottom of a lake, got out by pulling himself up by his bootstraps.